REMARKS

As amended above, claims 1-11, 14 and 19-24 are pending in this application. Claims 15-18 have been deleted; Applicants specifically reserve the right to file one or more continuation applications directed to the subject matter of these applications. Claims 19-22 have been withdrawn. Claims 19 and 21 have been amended to keep the scope of the claims consistent with the scope of claim 1. Claim 22 has been amended to reintroduce claim language inadvertently canceled in the previous amendment. Amendments to other claims are discussed below as part of the response to specific grounds of rejection set forth in the Office Action.

Claims 1-11 and 14-18 have been rejected under 35 U.S.C. §112, first paragraph, as not complying with the written description requirement on the basis that the terms "solvate" and "prodrug" are not defined in the specification. The claims also have been rejected under the second paragraph of this section of the statute, as being indefinite in their recitation of "solvate" and "prodrug" on the basis that the terms are not defined in the claims. For purposes of advancing the prosecution of this application, Applicants have deleted reference to these terms in the claims, thereby obviating these grounds of rejection.

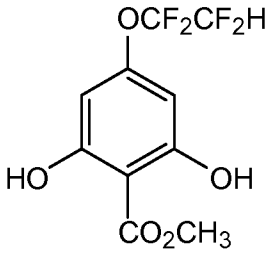
The rejection of claims 15-18 under 35 U.S.C. §112, second paragraph, has been rendered moot by the cancellation above of these claims.

The examiner also asserted that claims 1 and 10 are drawn to acids, solvates or prodrugs, while claims 23 and 24 are drawn to the acids a second time. The examiner advocated canceling claims 23 and 24 to overcome this rejection.

Applicants respectfully submit that claims 23 and 24 do not need to be canceled. The two sets of claims are not of equivalent scope. As amended, claims 1 and 10 are directed to a generic class of compounds and their salts and to a specific compound and its salts, respectively; claims 23 and 24 are more narrowly directed to the same generic class of compounds and to the same specific compounds; they do not reference salts of the compounds. Applicants submit that both sets of claims properly can be maintained in the application.

All of the pending claims of the application have been rejected under 35 U.S.C. §102(b) as anticipated by Arnolds-Stanton et al., *J. Org. Chem.*, 56(1), 151-157 (1991). The examiner asserted that compound 13 anticipates the instant compounds and their compositions. This rejection is traversed.

Compound 13 of the Arnolds-Stanton reference is methyl 2,6-dihydroxy-4-(1,1,2,2-fluoroethoxy)benzoate, which has the structural formula:



This compound does not anticipate the compounds of claim 1. Claim 1 specifically provides that when R^1 is methyl, R^2 is hydrogen, R^3 is 1,1,2,2-tetrafluoroethyl and each of R^4 and R^5 is hydrogen, R^6 cannot be hydroxy. This proviso thus excludes from the scope of claim 1 the compound of the Arnolds-Stanton reference.

Claims 2-9 are dependent from claim 1 and so also are not anticipated by the Arnolds-Stanton reference. In addition, dependent claim 2 is further differentiated from the Arnolds-Stanton compound. Specifically, claim 2 provides that each of R^4, R^5 and R^6 is hydrogen; in compound 13 of Arnolds-Stanton, the substituent on the benzene ring which is equivalent to the R^6 position is a hydroxy group. To the extent that claims 3-5

depend from claim 2, they also have this further distinction. Claim 6 also is further distinguished from the reference compound in that it requires that R^3 is 2,2,3,3,3-pentafluoropropyl. The comparable substituent of compound 13 is 1,1,2,2-tetrafluoroethyl.

Claim 7 also is further distinguished from compound 13 of Arnolds-Stanton in that it requires that the substituent at the R^1 position is hydrogen; in compound 13 that substituent is a methyl group. Claim 9 is directed to a number of specific compounds, none of which corresponds with compound 13.

Independent claim 10 is directed to a single specific compound, 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid, or a salt thereof; this compound clearly is not anticipated by compound 13. Independent claim 11 also is directed to a single compound, 2-acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid, or a salt thereof; this compound also clearly is distinguished from compound 13.

Independent claim 14 is directed to a pharmaceutical composition comprising an effective amount of a compound of formula I, as defined, and at least one pharmaceutically acceptable excipient. This claim is not anticipated by the disclosure of compound 13 in the Arnolds-Stanton reference. The Arnolds-Stanton paper contains no disclosure or suggestion that

any of the compounds disclosed therein can be a component, along with a pharmaceutically acceptable excipient, of a pharmaceutical composition.

Independent claim 23 is directed to compounds of formula I, wherein formula I is defined as in claim 1. This claim is not anticipated by the disclosure of compound 13 in the Arnolds-Stanton reference. As pointed out above in the discussion of claim 1, formula I as defined specifically excludes a compound having the specific substituents on the benzene ring found in compound 13. Claim 24 is directed to a specific compound, 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid; this compound clearly is different from and, therefore, not anticipated by, compound 13.

As evidenced by the discussion above, the Arnolds-Stanton reference does not anticipate any of the pending claims of the present application.

All of the pending claims also have been rejected under 35 U.S.C. §102(b) as anticipated by the disclosures of U.S. Patent 5,374,772, issued to Carson et al. The examiner focused on the compounds of column 2, lines 35-50, and compositions comprising them, column 1, lines 38-40. This rejection is traversed.

Applicants note that the examiner asserted that the compounds of the '772 patent anticipated the prodrugs of the

claimed compounds. Applicants have deleted reference to prodrugs in their pending claims and so this basis for the rejection is moot.

The compounds of the pending claims are not anticipated by the '772 patent. The patent discloses a group of 2,4-disubstituted benzoic acid and benzoate compounds. None of the compounds disclosed, however, contain fluoroalkoxy substituents. This is in contrast to the compounds which are the focus of the present claims. Formula I, as defined in all of the independent claims, is directed to a group of compounds in which a C_{1-5} fluoroalkyl, C_{2-5} fluoroalkenyl or C_{2-5} fluoroalkynyl group is a substituent (R^3) which is bonded through an oxygen to the benzene ring. As the compounds of the '772 patent lack a key substituent of the present compounds, this patent does not anticipate any of the compounds claimed in the present application.

Claims 1-11, 14, 17 and 23-24 have been rejected under 35U.S.C. §102(b) as anticipated by the teachings of Mu et al., *Colloids and Surfaces A: Physicochem. Eng. Aspects* 181:303-313 (2001). The examiner asserted that the reference discloses ethyl 2,4-dihydroxybenzoate and that this compound anticipates the compounds of claims 1-2, 8-9, 14, 17 and 23 and the prodrugs and compositions of the compounds of claims 1-11, 14, 17 and 23-24. This rejection is traversed.

Applicants respectfully submit that the Mu et al. reference does not anticipate the present claims. As noted above, the claims no longer make reference to prodrugs, and so that basis for the rejection is now moot. The particular compound cited by the examiner does not anticipate any of the compounds of formula I as set forth in the independent claims of this application as it lacks a fluoroalkoxy substituent, and such a substituent is part of all of the compounds of the present invention. The Mu et al. reference does disclose three other compounds which do comprise fluoroalkoxy substituents (ethyl 2-hydroxy-4-(2-perfluorohexylethoxy)benzoate, ethyl 2-hydroxy-4-(2-perfluorobutylethoxy)benzoate and ethyl 2-hydroxy-4-(2-perfluorooctylethoxy)benzoate), but these compounds are not within the scope of the present claims. Formula I as defined in each of the independent claims provides that the fluoroalkoxy side chain has no more than 5 carbons; in each of the compounds of the reference the side chain contains a fluoroalkoxy side chain in excess of five carbons. The disclosure by Mu et al. thus does not anticipate any of the pending claims of this application.

All of the pending claims have been rejected under 35 U.S.C. §102(b) as anticipated by Hardcastle et al., *Tetrahed. Letters* 42:1363-1365 (2001). More specifically, the examiner asserted

that the reference discloses 3,5,6-trifluoro-4-(3-fluoropropoxy)-2-hydroxybenzoic acid (designated compound 1g) and that this disclosure anticipates the compounds of claims 1-5, 7-9, 14-17 and 23 and the prodrugs and compositions of claims 1-11, 14-18 and 23-24. This rejection is traversed.

Claim 1 specifically provides that when each of R^1 and R^2 is hydrogen and R^3 is 3-fluoropropyl, then R^4, R^5 and R^6 cannot simultaneously be fluoro. This proviso specifically excludes from the scope of claim 1 the compound disclosed by Hardcastle et al. The reference thus does not anticipate claim 1 or the claims which depend from it.

A number of the dependent claims are more specifically or further distinguishable over the Hardcastle reference. Claim 2 provides that each of R^4, R^5 and R^6 is hydrogen; in the compound disclosed by Hardcastle et al. each of the comparable positions is substituted with a fluoro group. To the extent that each of claims 3-5 depends from claim 2, this distinction applies as well. Claim 9 lists a number of specific, individual compounds, none of which is the compound disclosed by Hardcastle.

Independent claim 14 is directed to a pharmaceutical composition comprising a effective amount of a compound of formula I, as defined, and at least one pharmaceutically acceptable excipient. This claim is not anticipated by the

disclosure of the compound 1g in the Hardcastle et al. reference. The claim is directed to a pharmaceutical composition and the focus of the Hardcastle et al. paper is on the synthesis of a library of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids; there is no disclosure or suggestion that any of the compounds disclosed therein can be a component, along with a pharmaceutically acceptable excipient, of a pharmaceutical composition.

Independent claim 23 is directed to compounds of formula I, wherein formula I is defined as in claim 1. This claim is not anticipated by the disclosure of compound 1g. As pointed out above in the discussion of claim 1, formula I as defined specifically excludes a compound having the specific substituents on the benzene ring found in compound 1g.

All of the pending claims have been rejected under 35 §103 as unpatentable over each of the references by Arnolds-Stanton et al., Mu et al., and Hardcastle et al., taken individually. This rejection is traversed.

Applicants respectfully submit that the compounds of formula I as set forth in claim 1 are not rendered obvious by the Arnolds-Stanton reference. This reference discloses, in relevant part, one specific compound, compound 13, which has two hydroxy groups in positions meta to one another on the central benzene

ring. There is no suggestion of substituting any other group for either of the hydroxy groups, much less any of the specific groups provided at the R^6 position in the compounds of formula I of claims 1 or 23 of the present application. The focus of the Arnolds-Stanton paper was nucleophilic additions of aryloxides, in which the Krespan reaction was carried out on a dihydric phenol, a trihydric phenol and a fluoroolefin. Compound 13 was the reaction product of a four step reaction process in which the starting compound was the trihydric phenol phloroglucinol. There is nothing in this paper to suggest the compounds of formula I of the present application and one of skill in the art who had knowledge of this paper would have no reason to consider or to make any of the presently claimed compounds. The single compound disclosed in the reference, could, theoretically, be modified in any number of ways; there is nothing in the reference to suggest modifying it to arrive at any of the compounds of formula I. Applicants respectfully submit that a conclusion that the compounds of claim 1 and the claims dependent upon it or claim 23 are obvious in view of the teachings of this reference can only be based upon hindsight, and it is a well-established tenet of US patent law that hindsight is not the proper standard upon which obviousness should be based.

> To imbue one of ordinary skill in the art with knowledge of the invention ... when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.

Gore v. Garlock, 220 USPQ 303, 313 (Fed. Cir. 1983).

It should be noted that a number of the compound claims are directed to compounds with multiple differences from compound 13. For example, claim 10 is directed to the specific compound 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid or a salt thereof, and claim 24 is directed to that same compound. There is no suggestion of this compound in the Arnolds-Stanton reference. Similarly, there is no suggestion in the reference of the compound of claim 11, 2-acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid, or its salt.

The Arnolds-Stanton reference focuses on the synthesis of a number of compounds. There is no discussion of any use of the compounds produced. In contrast, claim 14 is directed to a pharmaceutical composition comprising a compound of formula 1 and at least one pharmaceutically acceptable excipient. Such compositions clearly are not rendered obvious by the Arnolds-Stanton reference.

Inasmuch as the Arnolds-Stanton reference discloses, in relevant part, only a single compound and provides no suggestions regarding possible modifications of that compound or uses of that compound, the reference does not render obvious the present claims.

The Mu reference provides a method for the synthesis and monolayer formation of liquid crystal polysiloxanes which have a side chain with a perfluoroalkyl chain. The reference teaches the formation of compounds useful in the preparation of fluorocarbon side chains for the desired polymers. The reference discloses three ethyl 2-hydroxy benzoates with a perfluoroalkyl ethoxy substituent at the 4 position, wherein in each instance the alkyl group has at least 6 carbons. The reference does not suggest the broad class of compounds of formula I of claim 1 or 23 of the present application. There is nothing in the reference which would lead one to make those compounds of formula I which are 2-hydroxy benzoates with a perfluoroalkoxy substituent; as Applicants already have pointed out, these compounds were simply the starting compounds for making monomers M1 - M3, following a four step synthesis, which, in turn, are intermediates in the production of desired polymeric compounds P1 - P3, and the reference indicates that increasing the perfluoroalkyl ethoxy

group from a total of 6 to 10 carbons results in polymers with enhanced properties.

The polymers of Mu et al. are said to be useful as liquid crystals. The paper indicates that polymers with longer fluoroalkyl chains work better--i.e. there is an enhancement effect on the collapse pressure. See the paragraph bridging columns 1 and 2 on page 311. The paper also concludes that the length of the perfluoroalkyl chains affects the stability of the monolayer and the packing of the side chains at the air-water interface and that strong interactions between long fluorocarbon chains are necessary to stabilize the layer structure in multilayer LB films. See the last paragraph of text on page 312. One reading this paper thus would come away with the conclusion that longer fluoroalkyl chains are desired, and as such the paper teaches away from considering starting material compounds with a fluorinated alkoxy chain of less than 6 carbons.

Mu et al. do not suggest any variations of their starting compounds, with the exception that the overall length of the fluorinated alkoxy group can vary from 6-10 carbons in length, and they provide no guidance regarding changes in chemical structure. Applicants note that claim 4 focuses on compounds in which R^3 is a C_{1-3} fluoroalkyl, C_{2-3} fluoroalkenyl or C_{2-3} fluoroalkynyl group. Claim 5 focuses on compounds in which R^3 is

a C_{1-3} fluoroalkyl group. These compounds have fluoroalkoxy substituents which are at least 3 carbons shorter than the fluoroalkoxy chains of the starting compounds disclosed by Mu et al., and there is no suggestion in the reference of such compounds or any motivation to make them. As noted above, in view of the teachings of the reference, any focus on modifying the starting compounds would be on compounds with longer fluoroalkoxy chains, not shorter chains. Claim 6 is directed to compounds in which R^3 is a 2,2,3,3,3-pentafluoropropyl group; the complete substituent thus is 2,2,3,3,3-pentafluoropropoxy. Such a substituent is not suggested by the Mu starting compounds; the Mu compounds not only require at least 3 more carbons in the fluoroalkyl group, but in each instance, regardless of how long the complete carbon chain, the first two carbons in the chain do not carry any fluoro groups. One would not be led from these compounds to the compounds of claim 6, in which not only is the carbon chain significantly shorter, but only the first carbon is unsubstituted by fluoro groups. Claims 9, 10 and 11 also are limited to compounds carrying either a fluorinated propoxy or fluorinated ethoxy group in which only the carbon directly bonded to the oxygen does not carry one or more fluoro groups. None of these compounds is suggested by the reference.

Claim 7 of the present application is directed to compounds in which R^1 is hydrogen. These compounds are further distinguished from the compounds disclosed by Mu et al., all of which carry an ethyl group at the comparable position. Claim 24 focuses on the specific compound 2-hydroxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid. This compound also is similarly further distinguished at the R^1 position from the compounds disclosed by Mu et al., as well as having a fluorinated alkoxy substituent distinctly different from those of the Mu et al. compounds. Claim 11, already mentioned above, focuses on 2-acetoxy-4-(2,2,3,3,3-pentafluoropropoxy)benzoic acid; it thus is further distinguished from the Mu et al. compounds in the presence of the acetoxy group, rather than a hydroxy group, at the R^2 position, as well as by a fluorinated alkoxy substituent distinctly different from those of the Mu et al. compounds. As Applicants have noted above, Mu et al. disclose only the three specific starting compounds; they do not suggest any variations and so there is nothing to lead one to any of the claimed compounds. It is only through hindsight that one can assert that the reference would lead one to the claimed compounds, and, as discussed above, hindsight is not the appropriate test for determining obviousness.

Claim 14 is directed to pharmaceutical compositions of compounds of formula I and at least one pharmaceutically acceptable excipient. As the relevant compounds of Mu et al. are taught only to be useful intermediates in the production of certain polymers, the reference does not render the pharmaceutical compositions of claim 14 obvious.

The third reference cited by the examiner in making the rejection under §103 is the paper by Hardcastle et al. The relevant single compound of the many compounds of the Hardcastle reference is 2-hydroxy-4-(3-fluoropropoxy)-3,5,6-trifluorobenzoic acid, a compound having three fluoro groups directly bonded to the central benzene ring at what would be the equivalent of the R^4, R^5 and R^6 positions of the compounds of formula I. There is no suggestion in this reference that any of those three fluoro groups can be replaced with any of the substituents listed for R^4, R^5 and R^6 of the general formula I in claim 1 or claim 23. Indeed, the focus of the paper is the preparation of a library of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids.

There certainly is no suggestion in the Hardcastle reference that all three fluoro groups can be replaced with hydrogens, as set forth in claim 2. Conversely, neither is there any suggestion that the majority of hydrogens of the 4-alkoxy group can be substituted by fluoro groups, as in the compound of claim

6 or 10 or 24. The compound of interest in the Hardcastle reference carries a single fluoro on the propoxy group; the compounds of claims 6, 10 and 24 carry a pentafluoropropoxy group. Nowhere does Hardcastle suggest a substituent carrying more than one fluoro group. The compound of claim 11 is further removed from the cited compound of Hardcastle et al. in that it carries an acetoxy group at the 2 position as well as an alkoxy group (propoxy group) which is highly substituted with fluoro groups (i.e., pentafluoropropoxy).

As noted above, Hardcastle et al. teach synthesizing a library of 4-alkoxy-2-hydroxy-3,5,6-trifluorobenzoic acids. The synthesis method is said to result in a library of compounds which of sufficient purity that they can be biologically evaluated as inhibitors of the enzyme farnesyl transferase. In the paragraph bridging pages 1364-1365, the authors state that products 1c-1m were assayed for activity versus farnesyl transferase and geranylgeranyl transferase I and that none of the compounds displayed activity against the target enzymes. The reference does not render obvious claim 14 of the present application which is directed to pharmaceutical compositions of the compounds of formula I with one or more pharmaceutically acceptable excipients.

Applicants thus respectfully submit that the pending claims are not unpatentable under § 103 in view of the cited references.

In addition to the foregoing rejections of the claims, the examiner objected to the specification on the basis that it does not contain all of the proper headings. This objection has been obviated by the amendments to the specification set forth above.

Applicants note that at the end of the Office Action the examiner noted that a certified copy of an English translation of the priority application is not in the file. Applicants are unaware of a need to have submitted such a certified copy; if one is required, Applicants ask that the examiner provide his reasoning.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the claims of the application are in condition for allowance.

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